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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,585	04/20/2007	Simon Richard Green	CC1-066US	7005

959 7590 05/07/2009

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EXAMINER	
OLSON, ERIC	

ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
05/07/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,585	GREEN ET AL.	
	Examiner	Art Unit	
	ERIC S. OLSON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/27/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This application is a national stage application of PCT/GB04/05081, filed December 3, 2004, which claims priority to foreign application GB0328180.5, filed December 4, 2003. Claims 1-31 are pending in this application and examined on the merits herein. Applicant's preliminary amendment submitted June 2, 2006 is acknowledged wherein claims 3-7, 10-13, 16, 20, 23-25, and 27 are amended.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 7 and 28-31 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7 and 28-31 provide for the use of a combination of two chemicals, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 1-4, 6-15, 17-26, and 28-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims are drawn to metabolites of 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-N4-palmitoyl-cytosine. The claims do not identify what metabolic system or systems are being used to produce the metabolites. For example, metabolites of 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-N4-palmitoyl-cytosine could refer to its *in vivo* metabolites produced in the human body. Alternatively the claims could refer to metabolites produced by contacting 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-N4-palmitoyl-cytosine with various metabolic systems *in vitro*, for example cell cultures, bacterial cultures, fungal cultures, or cell free enzymatic systems. As the scope of metabolic transformations preformed on these compounds is not defined, the claims are indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5-9, 12-20, 23-26, and 29-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods involving certain specific CDK inhibitors such as roscovotine, Purvalanol A or B, and olomoucine, does not reasonably provide enablement for methods comprising using all possible CDK inhibitors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a method involving administering a compound to a living subject. In order to be enabled to practice such methods, one skilled in the art must be able to obtain all of the required compounds. In some cases the compounds can be obtained commercially. If this is not possible they must be obtained in another way such as isolation as natural products or chemical synthesis.

The state of the prior art: Various CDK inhibitors, for example roscovitine, purvalanol A or B, and olomoucine, are known in the prior art. However, the prior art does not exhaustively recite every possible compound that is a CDK, CDK2, or CDK4 inhibitor, or provide some method for clear *a priori* determination of whether a compound inhibits these enzymes.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: The *in vivo* effects of a compound are determined by various interactions of the compound with a range of biological systems. Not all compounds that inhibit a given enzyme *in vitro* are useful as therapeutic agents. In addition, the enzyme inhibitory activity of a particular small molecule cannot necessarily be determined merely by contemplating the molecule's structure. While many compounds have similar biological activities to known compounds of similar structure, many other compounds do not possess sufficient structural similarity to known therapeutic compounds to allow one skilled in the art to predict their function without actually testing them for activity.

According to Silverman (Reference included with PTO-892, pp. 4-47) the process of drug discovery typically involves the discovery of a lead compound by random or nonrandom means, followed by extensive optimization of the lead to develop a therapeutic drug compound. Various modifications are carried out and tested on the different functional groups of the lead compound in order to determine which parameters effect the ultimate utility. This process requires extensive characterization and experimentation for each lead compound, and must be repeated every time a new

lead compound is developed. Clearly, there is no simple, predictable formula for producing new active compounds. Instead there is only the slow, unpredictable process of screening and optimization.

Furthermore, there exist many potential compounds that are difficult to obtain. Not all compounds that could be conceivably evaluated as therapeutic agents can be obtained commercially or synthesized without unpredictable experimentation. Rather, some of these compounds would require a difficult process of unpredictable experimentation in order to develop a novel synthesis whereby they could be manufactured. The art of organic synthesis is unpredictable in that there is no sure-fire formula that can be used to determine the proper synthetic route to a particular compound. Rather, developing a novel synthesis of a novel compound involves a process of unpredictable trial and error.

For these reasons the claimed invention is seen to be complex and unpredictable.

The Breadth of the claims: The claimed invention is very broad, encompassing a method involving administering to a subject **any compound whatsoever**, be it an organic small molecule, a polypeptide, polynucleotide, oligosaccharide, viral vector, inorganic complex, or other substance that happens to inhibit a CDK enzyme.

The amount of direction or guidance presented: The specification sates that the claimed cyano-arabino nucleosides produce a synergistic effect when combined with CDK inhibitors. The only CDK inhibitor specifically described in combination with these compounds or shown by experimental data to produce an antitumor effect in

combination with the compounds is roscovitine. However the specification does not provide a comprehensive listing of the full scope of CDK inhibitors or provide a method whereby one skilled in the art could discover and synthesize every possible CDK inhibitor.

The presence or absence of working examples: No working examples are provided for actual treatment of a tumor *in vivo*.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the discovery of novel compounds. See MPEP 2164.

The quantity of experimentation necessary: One of ordinary skill in the art, in order to practice the claimed invention with the full range of CDK inhibitors beyond the meager number disclosed in the specification would be required to test potential compounds *in vivo* to determine whether a particular compound is useful as a CDK inhibitor. According to the 2006 Chemical Abstracts catalog, (Reference included with PTO-892) The Chemical Abstracts Registry contains entries for approximately 26 million compounds, all of which are potentially included in the claimed invention if they happen to have CDK inhibitory activity. For most compounds, it is unknown whether they are or are not useful as CDK inhibitors. Gathering this data for every compound known to man would involve *in vitro* screening of an enormous diversity of chemical compounds for CDK inhibition and antitumor activity activity, as well as *in vivo* testing of compounds having this activity involving either human or animal subjects to determine therapeutic utility. *In vitro* testing requires that the compounds to be tested be synthesized and

subjected to an appropriate screening method. As described earlier, synthesis of diverse chemical structures requires novel and unpredictable experimentation in order to develop suitable synthetic methods. *In vivo* animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Human tests impose even greater ethical and regulatory burdens, as well as additional difficulty locating subjects. Because of the unpredictability of the art and the lack of comprehensive working examples covering any significant portion of the total number of potential antitumor CDK compounds, these animal experiments would need to be repeated hundreds of times, and involve the maintenance, killing, dissection, and disposal of thousands of experimental animals, to establish the activity or lack thereof of every possible CDK inhibitor, thus presenting an a burden of undue experimentation to anyone practicing the invention with the full range of CDK inhibitors claimed.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the lack of guidance or working examples, Applicants fail to

provide information sufficient to practice the claimed invention for all possible CDK inhibitors.

Claims 1-4, 6-15, 17-26, and 28-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific compounds 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-cytosine (CNDAC) and 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-N4-palmitoyl-cytosine does not reasonably provide enablement for all possible metabolites of Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-N4-cytosine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a method involving administering a compound to a living subject. In order to be enabled to practice such methods, one skilled in the art must be able to obtain all of the required compounds. In

some cases the compounds can be obtained commercially. If this is not possible they must be obtained in another way such as isolation as natural products or chemical synthesis.

The state of the prior art: 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-cytosine (CNDAC) and 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-N4-palmitoyl-cytosine are both known in the art to be antitumor drugs. It is also known that various enzymes transform drugs *in vivo* to produce metabolites which may have different activities than the compound originally administered to the patient. However, the prior art does not exhaustively disclose all of the possible metabolic pathways that affect 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-N4-palmitoyl-cytosine or the full scope of metabolites produced from this compound.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: The *in vivo* metabolism of drugs is complex and unpredictable. Once a drug enters the body it undergoes many different chemical transformations before it is eliminated, For example modification by kinases or P450 enzymes. Each of the metabolites produced in this manner is a distinct therapeutic entity which may or may not exert a pharmacological activity on the subject. There is no expectation that a metabolite of a drug will have the same activity as the parent compound, as it may be more or less active, or may produce an entirely different effect.

Furthermore it is not possible to predict *a priori* the types and amounts of all the metabolites that will be produced from a given compound. For example, Danesi et al.

(Reference included with PTO-892) discloses a number of different enzymes responsible for metabolism of chemotherapeutic drugs. (p. 423 left column last paragraph - p. 424 right column third paragraph) Given the complexity of drug metabolism, and the fact that the metabolic genes vary between individuals, one cannot Speak of "metabolites thereof" as a distinct, well-defined class of compounds.

For these reasons the claimed invention is seen to be complex and unpredictable.

The Breadth of the claims: The claimed invention is very broad, encompassing a method involving administering to a subject or an isolated cell **any compound whatsoever**, be it an organic small molecule, a polypeptide, polynucleotide, oligosaccharide, viral vector, inorganic complex, or other substance that happens to be derivable from 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-N4-palmitoyl-cytosine by a metabolic pathway.

The amount of direction or guidance presented: The specification indicates that 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-N4-palmitoyl-cytosine and one metabolite 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-cytosine are useful as antitumor drugs. However the specification does not provide a comprehensive listing of the full scope of metabolites of said compound or provide a method whereby one skilled in the art could discover and synthesize every possible metabolite.

The presence or absence of working examples: No working examples are provided for actual treatment of tumors *in vivo*.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the discovery of novel metabolites. See MPEP 2164.

The quantity of experimentation necessary: One of ordinary skill in the art, in order to practice the claimed invention with the full range of metabolites beyond the meager number disclosed in the specification would be required to fully and completely characterize the metabolism of 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-N4-palmitoyl-cytosine. As the metabolism of this compound has not been disclosed by the prior art, this undertaking would involve a great burden of undue and unpredictable research in order to identify and characterize all of the claimed metabolites.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for all possible metabolites of 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-N4-palmitoyl-cytosine.

Claims 1-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating certain specific cancers such

as colon, lung, and prostate cancer, does not reasonably provide enablement for methods and compositions comprising a method of treating any cancer whatsoever or any proliferative disorder whatsoever. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is drawn to a method of treating any proliferative disorder whatsoever by administering a combination of two active agents. In order to be enabled for practicing a therapeutic method, one skilled in the art must have a reasonable expectation of success in treating any of the claimed diseases using the disclosed therapeutic methods.

The state of the prior art: The prior art discloses various proliferative disorders, which can be treated by certain specific active agents. However, the prior art does not disclose a single compound or therapeutic regimen that is reasonably expected to treat

all possible proliferative disorders. (e.g. all cancers, psoriasis, warts, granulomas, fibroids, pre-malignant polyps)

With regards to generalizing specific results to the treatment of all cancers, the skilled artisan would view cancer as a group of maladies not treatable with one medicament or therapeutic regimen. No single therapy is useful for the treatment of every case of cancer. Indeed, some types of cancer to not respond well to any known chemotherapeutic drugs. According to the Merck Manual of Diagnosis and Therapy (Reference included with PTO-892), Hepatocellular carcinomas and renal cell carcinomas are not generally improved by chemotherapy. Acute lymphoblastic leukemia, on the other hand, responds well to a number of drugs, including vincristine, anthracyclines, and aspariginases, while acute mylogenous leukemia, on the other hand, responds to fewer drugs and is usually treated with cytarabine in combination with daunorubicin or idarubicin. Breast cancer, on the other hand, is best treated with surgery and/or radiation, but the prognosis can be improved by the addition of adjuvant chemotherapy. While results for antibody-based therapies are less completely studied, there is no reason for one skilled in the art to expect that tumors will display less heterogeneity with respect to antibody therapy.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: As mentioned above, no single treatment is effective for all cancers. Different cancers vary widely in their response to different chemotherapy regimens. According to the Oxford Textbook of Oncology, (Reference cited in PTO-892) “The important criteria for the tumor include its sensitivity

to cytostatic drugs, its clinical stage and its mass, the presence of measurable lesions or biochemical markers, and, finally, growth characteristics," as well as, "*In vitro* sensitivity tests have been disappointing. They predict well for resistance but are of little use for sensitivity," (p. 451, right column, second paragraph) and, "For many types of cancer the potential benefit of chemotherapy has not been demonstrated in well-designed clinical trials."

Based on the known teachings of the prior art such as that stated above, one skilled in the art would recognize that it is highly unpredictable in regard to the treatment in the instant case, including treating numerous and various tumors: gynecological tumors, ovarian carcinomas, testicle tumors, prostate carcinomas, skin cancer, kidney cancer, bladder tumors, esophagus carcinomas, stomach cancer, rectal carcinomas, pancreas carcinomas, thyroid cancer, adrenal tumors, various types of leukemia and lymphomas, Hodgkin's disease, tumor illnesses of the CAN, soft-tissue sarcomas, bone sarcomas, benign and malignant mesotheliomas, especially intestine cancer, liver cancer, breast cancer, bronchial and lung carcinomas, melanomas, acute and chronic leukemias and benign papillomatosis tumors, by performing the necessary experimentation to develop an optimized dose-dense protocol for treating said cancers.

There are compounds that treat a range of cancers, but no compound has been discovered that is effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. The treatment of cancer is highly unpredictable due to the differing forms of cancerous cells, their location, their potential for metastases, the fact that cancer

therapeutics are palliative rather than curative and that cancer treatment readily harms normal tissues. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers or tumor cells generally by enhancing the effectiveness of antibodies generally or the wherein the antibody is capable of activating complement or dependent cell-mediated cytotoxicity.

Furthermore with regard to treatment of other proliferative disorders, the typical therapies for the treatment of non-malignant proliferative disorders such as warts or psoriasis are vastly different from that involved in the treatment of cancer based on the different risks and benefits involved. Because cancer is uniquely deadly and difficult to treat, those skilled in the art routinely administer dangerous therapies with severe side effects and risk of death in an attempt to aggressively treat the cancer. On the other hand, benign proliferative disorders are treated much less aggressively due to their much lower severity. For example, warts and psoriasis are not fatal and merely impact the patient's quality of life, so any therapy having side effects on the order of those caused by cancer treatment would likely have a greater impact on the patient's quality of life than the disease itself. Thus treatments of malignant and non-malignant

proliferative disorders are two different fields of therapy and will typically use different methods. Thus a disclosure of treatment of cancer does not enable treatment of benign proliferative disorders.

Note that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

The Breadth of the claims: The claimed methods and compositions include methods and compositions capable of treating any proliferative disorder whatsoever, regardless of cause, parent cell type, genetic profile, and therapeutic resistance.

The amount of direction or guidance presented: Applicant's specification states that two compounds 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-cytosine (CNDAC) and 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-N4-palmitoyl-cytosine can be combined with CDK inhibitors for treating cancer, and additionally discloses *in vitro* data for inhibition of colon, lung, and prostate cancer cell lines. However, Applicant's specification does not define the limits of this therapy or provide a reasonable basis by which one skilled in the art may conclude that it is generally applicable to all cancers, much less all proliferative diseases.

The presence or absence of working examples: No working examples are disclosed for the actual treatment of disease in a living host.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the broad-spectrum treatment of cancer. See MPEP 2164.

The quantity of experimentation necessary: : In order to use the disclosed information to practice the claimed invention for a wide range of cancers, a skilled practitioner of the art would have to validate the therapeutic agents against a wide variety of targets, against which neither the prior art nor Applicant's specification gives any indication that they are useful. This would involve a process of optimizing and testing various regimens *in vivo* for each type of cancer or other proliferative disorder being treated. Because the art is still undeveloped, this process would involve unpredictable experimentation which would constitute an undue experimental burden on the practitioner.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the unpredictability of the art and the lack of guidance and working examples, Applicants fail to provide information sufficient to practice the claimed invention for the treatment of all possible proliferative disorders.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6-15, 17-26, and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kameko et al. (US patent 5691319, cited in PTO-892) in view of Altieri et al. (PCT international publication WO03/039536, reference included with PTO-1449)

Kameko et al. discloses antitumor compounds having a structure that includes 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-N4-palmitoyl-cytosine. (column 1 line 56 - column 2 line 67) These compounds can be used in a method of treating tumors. (column 3 lines 37-52) Preferred compounds include 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-N4-palmitoyl-cytosine. (Formula I-I in column 24 lines 29-45, embodiment I-1-11 in column 25) Test compounds including compound I-11are disclosed to have antitumor activity against p-338 leukemia cells. (column 111 line 34 - column 113 line 23) The compounds can be used in combination with a pharmaceutically acceptable carrier. (column 3 lines 37-43) Kameko et al. does not disclose a method further comprising administering a CDK inhibitor, for example roscovitine.

Altieri et al. discloses a method of treating a tumor comprising administering a mitosis-disrupting compound and a CDK1 antagonist, for example Pulvalanol A or B,

olomoucine, or roscovitine. (p. 8 paragraph 0029 - p. 9 paragraph 0032) Note that according to p. 2 lines 2-3, roscovitine is included within the definition of CDK2 inhibitors in the present invention. These compounds can be used in compositions with various pharmaceutically acceptable carriers. (p. 26 paragraphs 0106 and 0107)

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer both 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-N4-palmitoyl-cytosine as described by Kameko et al. and a CDK inhibitor such as roscovitine to a patient suffering from cancer, for example leukemia, in a composition comprising a pharmaceutically acceptable carrier. One of ordinary skill in the art would have been motivated to administer this combination because both active agents are disclosed to be useful for the same purpose, namely treating various cancers. One of ordinary skill in the art would have reasonably expected success because combining two known active agents which are known in the art to be useful individually against a particular condition is ordinary and routine in the art, particularly for the treatment of cancer, where multidrug regimens are commonplace.

As regards the limitation that the two components be administered in either therapeutically effective (claim 23) or subtherapeutic (claim 24) amounts, one of ordinary skill in the art would have expected the combination of these two agents to produce an additive therapeutic effect. Therefore one of ordinary skill in the art would have recognized that they could be administered in their normal therapeutic amounts, or alternatively that they could be administered in subtherapeutic amounts in order to produce the same therapeutic effect as the monotherapy with a reduced occurrence of

adverse effects. Furthermore arriving at the optimal therapeutic dose for a given compound is well within the ordinary and routine level of skill in the art.

Therefore the invention taken as a whole is *prima facie* obvious.

Claims 1-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanaoka et al. (Reference included with PTO-1449) in view of Altieri et al. (PCT international publication WO03/039536, reference included with PTO-1449)

Hanaoka et al. discloses the antitumor activity of the compounds CS-682 and CNDAC, which are the same compounds 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-cytosine (CNDAC) and 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-N4-palmitoyl-cytosine (CS-682) recited in the instant claims. (p. 227, left column third paragraph - p. 228 right column fourth paragraph) These compounds are useful for killing a variety of tumor cell lines including gastric, lung, mammary, colon, epidermoid, and ovarian tumors. (p. 229 table 1 at top of page) Hanaoka et al. does not disclose a method further comprising administering a CDK inhibitor, for example roscovitine.

Altieri et al. discloses a method of treating a tumor comprising administering a mitosis-disrupting compound and a CDK1 antagonist, for example Pulvalanol A or B, olomoucine, or roscovitine. (p. 8 paragraph 0029 - p. 9 paragraph 0032) Cancers treatable in this manner include for example lung, colon, breast, pancreatic, and prostate cancer, for example. Note that according to p. 2 lines 2-3, roscovitine is included within the definition of CDK2 inhibitors in the present invention. These

compounds can be used in compositions with various pharmaceutically acceptable carriers. (p. 26 paragraphs 0106 and 0107)

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer both 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-cytosine (CNDAC) or 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-N4-palmitoyl-cytosine (CS-682) as described by Hanaoka et al. and a CDK inhibitor such as roscovitine to a patient suffering from cancer, for example breast, ovarian, or lung cancer, in a combination comprising a pharmaceutically acceptable carrier. One of ordinary skill in the art would have been motivated to administer this combination because both active agents are disclosed to be useful for the same purpose, namely treating various cancers. One of ordinary skill in the art would have reasonably expected success because combining two known active agents which are known in the art to be useful individually against a particular condition is ordinary and routine in the art, particularly for the treatment of cancer, where multidrug regimens are commonplace.

As regards the limitation that the two components be administered in either therapeutically effective (claim 23) or subtherapeutic (claim 24) amounts, one of ordinary skill in the art would have expected the combination of these two agents to produce an additive therapeutic effect. Therefore one of ordinary skill in the art would have recognized that they could be administered in their normal therapeutic amounts, or alternatively that they could be administered in subtherapeutic amounts in order to produce the same therapeutic effect with a reduced occurrence of adverse effects.

Furthermore arriving at the optimal therapeutic dose for a given compound is well within the ordinary and routine level of skill in the art.

Therefore the invention taken as a whole is *prima facie* obvious.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERIC S. OLSON whose telephone number is (571)272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Eric S Olson/
Examiner, Art Unit 1623
5/4/2009